UNITED STATES DEPARTMENT OF COMMERCE
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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
08/869,406	06/05/97	BARNIKOL W	DT-2179

HM12/0504

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EXAMINER	
GUPTA, A	
ART UNIT	**PAPER NUMBER**
1653	28

DATE MAILED: 05/04/00

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary

Application No.	Applicant(s)
08/896,406	Wolfgang Barnikol
Examiner	**Group Art Unit**
Anish Gupta	1653

☒ Responsive to communication(s) filed on *Dec 20, 1999*.

☐ This action is **FINAL**.

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire *three* month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) *6-16* is/are pending in the application.

Of the above, claim(s) _____ is/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) *6-16* is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐approved ☐disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____.

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____.

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☐ Notice of References Cited, PTO-892

● Information Disclosure Statement(s), PTO-1449, Paper No(s). 27, 16, 18

☐ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

--- *SEE OFFICE ACTION ON THE FOLLOWING PAGES* ---

DETAILED ACTION

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claim Rejections - 35 USC § 102

1. Claims 6-14 and 16 are rejected under 35 U.S.C. 102(b) as being anticipated by Potzschke et al. (U) for the reasons set forth in the previous office actions and the reasons set forth below.

Applicants argue the following points:

a) At the time Potzschke et al. was published, the molecular structure of the hemoglobin polymers was not known in electrolyte solution. Therefore, the reference cannot disclose fractionation of hemoglobin polymer with gel permeation chromatography according to polymers molecular weights. The molecular weights recited in the reference were estimates and were better defined in a later published article by Postzschke et al. Moreover, "although the hydrodynamic volume fractions are molecular weights factions, the 'molecular weights' of hemoglobin polymers given in Potzschke are, in part extremely wrong since they have been made in accordance with native proteins, but not in accordance with the correct structures-in-solution, as it has been found out later."

b) Applicants again argue that the reference is only concerned with analytical method. "The substance fractions of the reference formed by analytical method during work are not separated fractions, **further useable** for other purposes. Moreover scale up of an analytical method to a distinct large preparative scale is often accompanied by a loss of performance and, in some cases, scale up therefore is impossible The degree of scale-up which is possible is not foreseeable, but must be determined experimentally."

Potzschke reference is not concerned with purification of the cross-linked hemoglobin by using Sephacryl S-400 gel as stated in the office action. This is because the cross-linked hemoglobin are stable and can be purified by ultrafiltration. Moreover, Applicants state that the reaction of the hemoglobin with specific cross-linking agent did lead to hemoglobin hyper polymers which did not show any changes in molecular size distribution as determined by size exclusion chromatography. Applicants also state that in the present method, it has been found that cross linking hemoglobin compounds with specific intrinsic viscosities are separated into fractions of different molecular weights

because the intrinsic viscosity of the respective molecular weight fractions are very similar. This could not be expected in the reference of record since the cross-linking reaction between hemoglobin and specific cross linking agents lead to hemoglobin polymers with broad size distribution.

Applicant's arguments filed 03-30-98 have been fully considered but they are not persuasive.

It should be noted the specification states "[h]uman hemoglobin was cross linked with the help of gluterdialdehyde to hyper polymers in accordance with a known protocol (Poetzschke, Barnikol, Biomater. Art. Cells and Immob. Biotechn., 20, (1992), 287-291)." (See page 12 of the specification) This reference is the Potzschke et al. reference recited in the rejection against the claims above. Therefore, reaction yielding the hemoglobin hyper polymers, in both the reference and the instant application, is the same. The reference also teach that the reaction material, after filtration and reduction, is subjected to gel chromatography using Sephacryl S-400. Applicants have stated that Potzschke is not concerned with purification of the cross-linked hemoglobin by using Sephacryl S-400 gel as stated in the office action. Although the reference may not be "concerned" with purification using Sephracryl S-400, the reference never the less teaches the method purification using such a gel. Note that Applicants' arguments regarding the chromatogram further support the fact that the reference teach the isolation of hemoglobin hyper polymers using the Sephracryl S-400. Therefore the claimed limitations have been met for the reasons set forth in the previous office actions.

Applicants also argue that the molecular weights of the reference are different from that of the instant application in that the molecular weights of hemoglobin polymers given in Potzschke are, in part extremely wrong since they have been made in accordance with native proteins, but not in accordance with the correct structures-in-solution. However, since the reference and the claimed method utilize the same reaction method to obtain the hemoglobin hyper polymers and both subject the reaction mixture to gel chromatography, using the same gel, and the same buffer (buffer containing NaCl, Hepes Buffer, and NaN3), the molecular weights would necessarily have to be the same. It has been held that the claiming of a new use, new function or unknown property which is inherently present in the prior art does not necessarily make the claim patentable (562 F.2d 1252, 1254,<195 USPQ 430, 433 (CCPA 1977). See also MPEP §

2112.01 with regard to inherency and product by process claims and MPEP § 2141.02 with regard to inherency and rejections under 35 U.S.C. 103).

Applicants have again stated that the claimed invention is a preparative method and thus the prior art does not anticipated them. However, the claims do not limit the scope as a preparative method, rather the claims rejected correspond to either a preparative method or an analytical method.

Note that claims 9 and 10 have been added to the rejection. The reference teach an electrolyte I solution (125 mmol/l NaCl, 4.5 mmol/l Kcl, 20 mmol/l NaHCO3, and 3 mmol/l NaN3) and Sephacryl S-400 high resolution gel buffer having a concentration of 144 mmol/l NaCl, 10 mmol/l HEPES buffer, and 3 mmol/l NaN3 as the eluent. Both of these buffer solutions have the same concentration of claim 9, 10, and 15.

Rejection is maintained.

Claim Rejections - 35 USC § 103

2. Claims 6-10 remain rejected and newly added claims 11-16 are under 35 U.S.C. 103(a) as being unpatentable over Potzschke et al.(U) in view of Bonhard et al. for the reasons set forth in the previous office actions and the reasons set forth below.

Applicants argue that the starting material of the present invention are not native hemoglobin but already crosslinked materials which are treated according to the present invention to obtain the molecularly uniform hyper polymeric hemoglobin. Moreover, the final product is not the hemoglobin cross linked with glutaraldehyde, but molecularly uniform hyper polymeric hemoglobin (cross linked with glutaraldehyde). The method according to Bonhard et al. involves the removal of monomeric hemoglobin and not polymerized hemoglobin. Applicants also argue that "in view of the known separation of non cross linked hemoglobin having a completely different structure from the very highly polymer hyper hemoglobin and, therefore, having completely different properties of their physical and chemical behavior, it could not have been expected that an agent which is said to be capable of separating two completely different compounds, could also be used to separate compounds which are chemically and physically similar in their behavior such as the hyper polymer hemoglobin of different molecular weights."

Applicant's arguments filed 2-8-99 have been fully considered but they are not persuasive.

The reference of Potzschke et al. has been discussed supra. As stated above, the specification states "[h]uman hemoglobin was cross linked with the help of gluterdialdehyde to hyper polymers in accordance with a known protocol (Poetzschke, Barnikol, Biomater. Art. Cells and Immob. Biotechn., 20, (1992), 287-291)." (See page 12 of the specification). The reference teach that the reaction was carried by subjecting 30 g/l of hemoglobin with GDA solution. The reaction was carried out for five hours and after filtering crosslinked hyper polymers were obtained. Therefore the starting material was native *non-crosslinked* hemoglobin. Applicants have stated that the starting material was crosslinked, however the Potzschke et al., which the specification relies upon, would seem to contradict this. Since the starting material was native hemoglobin, one of ordinary skill in the art would use ammonium sulfate to separate uncross-linked hemoglobin from cross-linked hemoglobin. Although it is unclear, Applicants seem to indicate the difference between the products of Bonhard et al. and the instant application. However, both products are crosslinked with a similar cross linking agent with the difference in the instant application being in the degree of cross-linking to obtain hyper polymeric hemoglobin with higher molecular weights. Accordingly one would expect the non-crosslinked hemoglobin to separate out from the cross-linked hemoglobin as taught in Bonhard et al.

Rejection maintained.

New Grounds For Rejection

3. Claim 9 and 10 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

Claim Rejections - 35 USC § 112

4. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 9, 10 and 15 rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 10 and 15 recites the limitation "electrolyte" in the base claims. However, there is insufficient antecedent basis for this limitation in claim 6 and 11. Note that claim 10 has been included in the rejection even thought it is dependent on claim 5 because it is assumed that the depedencey of claim 10 will be changed to claim 6.

Claims 9 and 10 are indefinite since the claims are dependent upon canceled claims.

Claim Rejections - 35 USC § 103

5. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

6. Claims 11 and 15 are rejected under 35 U.S.C. 103(a) as being unpatentable over Potzschke et al.

The claims are drawn to a method of preparation of molecularly uniform hyperpolymeric hemoglobin wherein the method comprises as performing *at least one of the steps* of either fractional precipitation in (NH4)2SO4 or fractionating chromatographically, or performing a partial fractional dissolution of the solution. The method further comprises the addition of a crosslinking agent such as glutaraldehyde.

The reference teaches the crosslinking of hemoglobin with glutaraldehyde and then purifying the product with Sephacryl s-400 high resolution gel (see Materials and Methods). The disclosed method initially wash the hemoglobin with an electrolyte I solution (125 mmol/l NaCl, 4.5 mmol/l Kcl, 20 mmol/l NaHCO3, and 3 mmol/l NaN3), then crosslink the hemoglobin with glutaraldehyde, then purifying the product with Sephacryl S-400 high resolution gel with a 144 mmol/l NaCl, 10 mmol/l HEPES buffer, and 3 mmol/l NaN_3 as the eluent electrolyte solution. The difference between the reference and the instant application is that the reference does not teach the exact concentration of Sephacryl S-400 buffers claimed, wherein claim 14 recites the use of a buffer having 1.5 mmol/L of NaN_3.

However generally, differences in concentration or temperature will not support the patentability of subject matter encompassed by the prior art unless there is evidence indicating such concentration or temperature is critical. "[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation."

7. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Anish Gupta whose telephone number is (703) 308-4001. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christopher Low, can normally be reached on (703)308-2923. The fax phone number of this group is (703) 308-4242.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Anish Gupta

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